

## NEW ZEALAND DATASHEET

### Fluohexal

*Fluoxetine Hydrochloride Ph Eur, powder filled capsule, 20 mg (as fluoxetine)*

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#### Presentation

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Capsule, powder filled, Size 3, opaque light green body and cap. Each capsule contains fluoxetine hydrochloride equivalent to fluoxetine 20 mg.

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#### Uses

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##### **Actions**

Fluohexal is a formulation of fluoxetine, an antidepressant intended for oral administration.

##### **Pharmacotherapeutic group**

N06AB03 – selective serotonin reuptake inhibitors (SSRIs), fluoxetine.

##### **Mechanism of action**

Fluoxetine is a selective inhibitor of serotonin reuptake, its presumed mechanism of action.

##### **Pharmacodynamic effects**

The antidepressant and antiobsessional action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in humans have demonstrated that fluoxetine blocks the uptake of serotonin, but not of noradrenaline, into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of noradrenaline.

Fluoxetine has practically no affinity to other receptors such as alpha1-, alpha2- and beta-adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors. Antagonism of these receptors has been hypothesised to be associated with the various anticholinergic, sedative and cardiovascular effects of classic tricyclic antidepressant drugs.

##### *Premenstrual dysphoric disorder (PMDD)*

The aetiology of premenstrual dysphoric disorder is unknown, but endogenous steroids (neuro and/or ovarian) involved in the menstrual cycle may interrelate with neuronal serotonergic activity. In clinical trials fluoxetine was shown to be effective in relieving both the cyclical mood changes and physical symptoms (tension, irritability and dysphoria, bloating and breast tenderness) associated with PMDD.

##### **Pharmacokinetics**

###### **Absorption**

Fluoxetine is 80 to 95% absorbed following oral administration. In humans, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/ml are observed after 6 to 8 hours. There is a linear dose proportionality for the absorption of fluoxetine over the therapeutic dose range.

Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at four to five weeks.

Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus fluoxetine may be administered with or without food.

### **Distribution**

Fluoxetine is widely distributed; the volume of distribution is estimated at 30 to 40 l/kg.

Fluoxetine is extensively bound to plasma proteins. Over the concentration range from 200 to 1000 ng/ml, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins, including albumin and alpha1-glycoprotein. The interaction between fluoxetine and other highly protein bound drugs has not been fully evaluated, but may be important.

### **Biotransformation**

Fluoxetine is extensively metabolised in the liver to norfluoxetine and a number of other, unidentified metabolites which are excreted in urine. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, the potency and selectivity of norfluoxetine as a serotonin uptake blocker are essentially equivalent to those of fluoxetine. Multiple cytochrome P450 isoenzymes, including CYP2D6, are responsible for the conversion of fluoxetine to norfluoxetine; thus other nonsaturable oxidative pathways (i.e. non-2D6 pathways) contribute considerably to norfluoxetine formation.

### **Elimination**

The elimination half-life of fluoxetine is 4 to 6 days and that of its active metabolite is 4 to 16 days.

#### *Clinical issues related to accumulation and slow elimination*

The inherent slow elimination of fluoxetine and the implications for accumulation may potentially affect its clinical use.

The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and four to six days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/ml and norfluoxetine in the range of 72 to 258 ng/ml have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single dose studies, presumably because its metabolism is not proportional to dose. Norfluoxetine however appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Thus even if patients are given a fixed dose, steady state plasma concentrations are only achieved after continuous dosing for weeks. Nevertheless, plasma concentrations do not appear to increase without limit. Specifically, patients receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years exhibited, on average, plasma concentrations similar to those seen among patients treated for 4 or 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine ensure that, even when dosing is stopped, active drug substance will persist in the body for weeks, primarily depending on individual patient characteristics, previous dosing regimen and length of previous therapy at discontinuation. This is of potential consequence when drug withdrawal is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine hydrochloride.

### **Indications**

Depression and its associated anxiety, bulimia nervosa, obsessive-compulsive disorder and premenstrual dysphoric disorder - a severe form of PMS.

### **Diagnosis of PMDD**

The essential features of PMDD are clear and established cyclicity of symptoms (occurring during the last week of the luteal phase in most menstrual cycles) such as depressed mood, anxiety, affective lability, and physical symptoms such as breast tenderness or swelling, headaches, joint or muscle

pain, bloating, and weight gain. PMDD is a severe clinical entity and is distinguished from the broader premenstrual syndrome by the intensity of its symptoms (particularly mood symptoms) and the extent to which it interferes with social and/or occupational function.

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## Dosage and administration

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### ***Depression***

20 mg per day is the recommended initial dose.

### ***Bulimia nervosa***

60 mg per day is the recommended dose.

### ***Obsessive-compulsive disorder***

20 mg to 60 mg per day is the recommended dose.

### ***Premenstrual dysphoric disorder***

20 mg per day is recommended continuously throughout the menstrual cycle. Initial treatment should be limited to six months, after which patients should be reassessed regarding the benefit of continued therapy.

### ***All indications***

The recommended dose may be increased or decreased. Doses above 80 mg per day have not been systematically evaluated.

### ***Age***

There are no data to suggest that alternate dosing is required on the basis of age alone.

### ***Use in children and adolescents (under 18 years of age)***

While clinical studies have been conducted in children and adolescents, the use of fluoxetine is not recommended in this population. (see Warnings and precautions – clinical worsening and suicide risk, impairment of fertility, Adverse effects)

### ***Administration with food***

Fluoxetine may be administered with or without food.

### ***Concurrent disease and/or concomitant medication***

A lower or less frequent dose should be considered in patients with hepatic impairment, with concurrent diseases, or who are taking multiple medications.

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## Contraindications

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### ***Hypersensitivity***

Fluoxetine is contraindicated in patients known to be hypersensitive to fluoxetine.

### ***Monoamine oxidase inhibitors***

Fluoxetine should not be used in combination with a monoamine oxidase inhibitor (MAOI) or within a minimum of 14 days of discontinuing treatment with a MAOI. At least five weeks should elapse

between discontinuation of Fluohexal and initiation of therapy with a MAOI. If Fluohexal has been prescribed chronically and/or at a high dose, a longer interval should be considered. Serious and fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome) have been reported in patients treated with fluoxetine and a MAOI in close temporal proximity.

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## Warnings and precautions

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### **Warnings**

#### **Clinical worsening and suicide risk**

The risk of suicide attempt is inherent in depression and other psychiatric disorders and may persist until significant remission occurs. As with other drugs with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during fluoxetine therapy or early after treatment discontinuation. This risk must be considered in all depressed patients.

Although a causal role for fluoxetine in inducing such events has not yet been established, some analyses from pooled studies of antidepressants in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviours in paediatric and young adult (<25 years of age) patients compared to placebo. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to closely monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Physicians should encourage patients of all ages to report any distressing thoughts or feelings at any time. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines SSRIs and others in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal

impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for fluoxetine should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

### **Mania and bipolar disorder**

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that fluoxetine is not approved for use in treating bipolar depression.

### **Rash**

Rash, anaphylactoid events, and progressive systemic events, sometimes serious and involving skin, kidney, liver or lung have been reported in patients taking fluoxetine. Upon the appearance of rash, or of other possible allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

## ***Precautions***

### **Seizures**

As with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures.

### **Hyponatraemia**

Cases of hyponatraemia (some with serum sodium lower than 110 mmol/l) have been reported. The majority of these cases occurred in elderly patients and in patients treated with diuretics or otherwise volume-depleted.

### **Glycaemic control**

In patients with diabetes, hypoglycaemia has occurred during fluoxetine therapy and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when fluoxetine therapy is initiated or discontinued.

### **Mydriasis**

Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of narrow-angle glaucoma.

### **Withdrawal reactions**

Withdrawal effects may occur and the dosage may need to be tapered on withdrawal in some patients. Discontinuation symptoms have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Because of the long elimination half-life of fluoxetine, and its active metabolite norfluoxetine, plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which reduces greatly the likelihood of developing discontinuation symptoms and makes dosage tapering unnecessary in most patients. Common symptoms associated

with withdrawal of SSRIs include dizziness, paraesthesia, headache, anxiety and nausea. Onset of symptoms can occur within a day of discontinuation but may be delayed, particularly in the case of fluoxetine, due to its long half-life. The majority of symptoms experienced on withdrawal of SSRIs are non serious, self-limiting and have varying durations. Fluoxetine has been only rarely associated with such symptoms.

### **Haemorrhage**

There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRIs. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other haemorrhagic manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients with a history of bleeding disorders as well as in patients taking SSRIs particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs) or other drugs that may increase risk of bleeding.

### ***Pregnancy and lactation***

#### **Use in pregnancy**

Fluoxetine use should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Assigned Category C by the Australian Drug Evaluation Committee. This category includes medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. SSRIs including fluoxetine have had limited use in pregnancy without a reported increase in birth defects. The use of fluoxetine in the third trimester may result in a withdrawal state in the newborn infant.

Experimental animal studies do not indicate direct or indirect harmful effects, with respect to the development of the embryo or foetus or the course of gestation. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

The drug crosses the placenta.

Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. However, one meta-analysis suggests a potential risk of cardiovascular defects in infants of women exposed to fluoxetine during the first trimester of pregnancy compared to infants of women who were not exposed to fluoxetine.

At the end of pregnancy, caution should be exercised, as transitory withdrawal symptoms (e.g. transient jitteriness, difficulty feeding, tachypnea and irritability) have been reported rarely in the neonate after maternal use near term.

Neonates exposed to fluoxetine and other SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), late in the third trimester have been uncommonly reported to have clinical findings of respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Such events can arise immediately upon delivery and are usually transient. These features could be consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Recent data suggests the use of SSRIs, including fluoxetine, after the first 20 weeks of pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The data shows the absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1000 women, compared to 1 to 2 per 1000 women in the United States general population. These findings should be taken into account by the physician when making decisions whether to continue the use of SSRIs during pregnancy.

### **Labour and delivery**

The effect of fluoxetine on labour and delivery in humans is unknown.

### **Use in lactation**

Fluoxetine is excreted in human milk at levels approaching 14% of the maternal dose; its active metabolite, norfluoxetine, has a long half-life of one to two weeks and may accumulate in a breastfed infant. Therefore caution should be observed when fluoxetine is administered to nursing women.

### **Effects on ability to drive and use machines**

This medicine is likely to produce minor or moderate adverse effects. Psychoactive medicines may impair judgement, thinking, or motor skills. Patients should be advised to avoid driving a car or operating machinery until they are reasonably certain that their performance is not affected.

### **Other**

#### **Information for patients and their families**

Physicians are advised to discuss the following issues with patients for whom they prescribe fluoxetine:

Because fluoxetine may impair judgement, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter medicines, or alcohol.

Patients should be advised to inform their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicine's efficacy and safety when used in the treatment regimen proposed.

#### **Preclinical safety data**

##### *Carcinogenesis, mutagenesis, impairment of fertility*

There is no evidence of carcinogenicity or mutagenicity from *in vitro* or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg per meter squared basis) was not observed.

In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Other findings in rats administered 30 mg/kg included degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, and immaturity and inactivity of the female reproductive tract. Plasma levels achieved in these animals at 30 mg/kg were approximately 5 to 8 fold (fluoxetine) and 18 to 20 fold (norfluoxetine), and at 10 mg/kg approximately 2 fold (fluoxetine) and 8 fold (norfluoxetine) higher compared to plasma concentrations usually achieved in paediatric patients. Following an approximate 11 week recovery period, sperm assessments in the 30 mg/kg males only, indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation of testes and

epididymides of these 30 mg/kg males indicated that testicular degeneration was irreversible. Delays in sexual maturation occurred in the 10 mg/kg males and in the 30 mg/kg males and females. The significance of these findings in humans is unknown. Femur length at 30 mg/kg increased to a lesser extent compared with control rats.

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## Adverse effects

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Adverse reactions are dose-dependent and more common at higher doses than 20 mg per day.

### ***Associated with Discontinuation of Treatment:***

Fifteen per cent of approximately 4,000 patients who received fluoxetine hydrochloride in U.S. premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritis.

In obsessive compulsive disorder studies, 12.1% of fluoxetine treated patients discontinued treatment early because of adverse events. Anxiety and rash at incidences of less than 2% were the most frequently reported events.

### ***Events Observed During Therapy with Fluoxetine – Clinical Trials:***

The following events listed by body system have been observed. Very common adverse events are defined as those occurring on one or more occasions in at least 1/10 patients; common adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; uncommon adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients; very rare events are those occurring in less than 1/10000 patients. It is important to emphasise that, although the events reported did occur during treatment with fluoxetine, they were not necessarily caused by it.

#### Body as a whole

Very common: fatigue (includes asthenia)  
Common: allergic reaction, chills  
Uncommon: feeling abnormal  
Rare: photosensitivity reaction, serum sickness, anaphylactoid reaction, vasculitis  
Very rare: serotonin syndrome (neuroleptic malignant syndrome-like effects), mild intensity headache

#### Cardiovascular system

Common: palpitations, vasodilatation  
Uncommon: hypotension  
Very rare: orthostatic hypotension

#### Digestive system

Very common: diarrhoea, nausea  
Common: anorexia, dyspepsia, gastrointestinal disorder, mouth dryness, vomiting  
Uncommon: dysphagia  
Rare: oesophageal pain

#### Haemic and lymphatic systems

Uncommon: ecchymosis

#### Metabolic/nutritional disorders

Common: weight loss

#### Musculoskeletal system

Uncommon: twitching

#### Nervous system

Very common: anxiety, dizziness, headache, insomnia, nervousness, somnolence, tremor  
Common: abnormal dreams, decreased libido, sleep disorder, thinking abnormal  
Uncommon: akathisia, ataxia, balance disorder, bruxism, buccoglossal syndrome, depersonalisation, dyskinesia, manic reaction, myoclonus, seizures, psychomotor hyperactivity

#### Respiratory system

Common: yawn

#### Skin and appendages

Common: pruritus, rash, sweating, urticaria  
Uncommon: alopecia

#### Special senses

Common: abnormal vision, taste perversion  
Uncommon: mydriasis

#### Urogenital system

Common: abnormal ejaculation (male only), gynaecological bleeding (female only), impotence (male only), urinary frequency  
Uncommon: anorgasmia, breast pain, sexual dysfunction (occasional persistence after treatment discontinuation), impaired urination  
Rare: priapism/prolonged erection (male only)

#### Children and Adolescents

Common: epistaxis.

(Very rare) Weight loss and decreased height gain: As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, paediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height ( $p=0.004$ ) and 1.1 kg less in weight ( $p=0.008$ ) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in serum alkaline phosphatase levels.

In a retrospective matched control observational study with a mean of 1.8 years of exposure to fluoxetine, paediatric subjects treated with fluoxetine had no difference in growth (0.0cm) adjusted for expected growth in height from their matched, untreated controls (95% CI: -0.6 to 0.6,  $p=0.9673$ ). Limited evidence is available concerning the longer-term effects of fluoxetine on the development and maturation of children and adolescent patients. Height and weight should be monitored periodically in paediatric patients receiving fluoxetine.

### **Post-marketing experience**

The following events have not been reported in clinical trials of fluoxetine, but have been reported in clinical practice and are associated with fluoxetine therapy. These events are classified as either rare (occurring in less than 1 in 1000 patients), very rare (occurring in less than 1 in 10000 patients) or uncommon (occurring from 1 in 100 to 1 in 1000 patients).

#### **Body as a whole**

Very rare: angioedema; serotonin syndrome, erythema multiforme, malignant hyperthermia, Stevens-Johnson syndrome

#### **Cardiovascular**

Very rare: angioedema

### **Digestive system**

Very rare: abnormal hepatic function, aggravation of hepatic damage, hepatic failure/necrosis, idiosyncratic hepatitis

### **Endocrine system**

Very rare: inappropriate secretion of antidiuretic hormone

### **Haemic and lymphatic system**

Rare: haemorrhagic manifestations such as gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings (refer to Warnings and precautions)

Very rare: eosinophilia, thrombocytopenic purpura

### **Nervous system**

Uncommon: seizures

Very rare: oculogyric crisis, tardive dyskinesia, memory impairment

### **Skin and appendages**

Very rare: epidermal necrolysis

### **Urogenital system**

Very rare: enlarged clitoris, gynaecomastia

### **Special populations**

#### *Children*

Very rare: headache.

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## **Interactions**

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### ***Monoamine oxidase inhibitors***

Refer to [Contraindications](#).

### ***Medicines metabolised by Cytochrome P450IID6 isoenzyme***

Because fluoxetine has the potential to inhibit the cytochrome P450IID6 isoenzyme, therapy with medications that are predominantly metabolised by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment range of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

### ***CNS active medicines***

Changes in the blood levels of phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, lithium, imipramine and desipramine, and in some cases, clinical manifestations of toxicity have been observed. Consideration should be given to using conservative titration schedules of the concomitant medicine and monitoring of clinical status. Concomitant use with other serotonergic agents such as SNRIs, SSRIs, triptans or tramadol may induce serotonin syndrome.

### ***Protein binding***

Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another medicine that is tightly bound to protein may cause a shift in plasma concentrations of either medicine.

### ***Drugs that interfere with haemostasis***

Caution is advised in patients with a history of bleeding disorders as well as in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs) or other drugs that may increase risk of bleeding.

### ***Warfarin***

Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but increased bleeding, have been reported uncommonly when fluoxetine is co-administered with warfarin. As is prudent in the concomitant use of warfarin with many other medicines, patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

### ***Electroconvulsive therapy (ECT)***

There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

### ***Elimination half-life***

The long elimination half-lives of fluoxetine and its principal metabolite, norfluoxetine, are of potential consequence when medicines are prescribed which might interact with either substance following the discontinuation of fluoxetine.

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## **Overdosage**

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Contact the Poisons Information Centre on 0800 POISON or 0800 764766 for advice on management of overdose.

### ***Signs and symptoms***

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

### ***Management***

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. No specific antidote is known. Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple medicine involvement.

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## **Pharmaceutical precautions**

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### ***Instructions for use/handling***

Nil.

### ***Incompatibilities***

None known.

### ***Shelf Life and Special precautions for storage***

Store at or below 25°C. Protect from light and moisture. Store in the original package. Fluohexal capsules must be kept out of the reach and sight of children.

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### **Medicine classification**

Prescription Medicine.

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### **Package quantities**

Packs of 28 capsules in cartoned blister strips.

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### **Further information**

#### ***List of excipients***

Gelatin, titanium dioxide, iron oxide pigment, Patent Blue V, pregelatinised maize starch, dimeticone, erythrosine.

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### **Name and address**

Novartis New Zealand Limited  
Private Bag 65904 Mairangi Bay  
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Telephone: 0800 354 335

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### **Date of preparation**

12 December 2011